

What is claimed is:

1. A method for purifying plasmin comprising:

cleaving a plasminogen in the presence of a plasminogen activator to yield an active plasmin;

substantially removing the plasminogen activator from the active plasmin by binding the active plasmin to an active plasmin-specific absorbent material to form a bound plasmin, and eluting the bound plasmin with an excipient solution having a pH from about 2.5 to about 9.0 to form a plasmin solution; and

buffering the plasmin solution with a low pH, low buffering capacity agent to form a reversibly inactive acidified plasmin.

2. The method of claim 1, wherein the excipient solution has a pH from about 4.0 to about 7.5.

3. The method of claim 1, wherein the excipient solution has a pH of about 6.0.

4. The method of claim 1, wherein the active plasmin-specific absorbent material comprises benzamidine.

5. The method of claim 1, wherein the plasminogen activator is further removed by hydrophobic interaction.

6. The method of claim 1, further comprising nanofiltration of the plasmin solution.

7. The method of claim 6, wherein the nanofiltration is carried out using a filter membrane characterized by an average pore size of approximately 15 nm.

8. The method of claim 1, wherein the plasminogen is cleaved in the presence of at least one excipient that is an omega-amino acid.

9. The method of claim 1, wherein the plasminogen is cleaved in the presence of at least one omega-amino acid selected from the group consisting of lysine, epsilon amino caproic acid, tranexamic acid, poly lysine, arginine, and combinations thereof.
10. The method of claim 1, wherein the plasmin is eluted in a solution comprising at least one salt, the solution having a conductivity from about 5 mS to about 100 mS.
11. The method of claim 10, wherein the at least one salt is sodium chloride.
12. The method of claim 11, wherein the sodium chloride is present at a concentration of from about 50 mM to about 1000 mM.
13. The method of claim 11, wherein the sodium chloride is present at a concentration of about 150 mM.
14. The method of claim 1, wherein the plasminogen is cleaved using a catalytic concentration of a plasminogen activator that is selected from the group consisting of immobilized plasminogen activators, soluble plasminogen activators, and combinations thereof.
15. The method of claim 1, wherein the plasminogen activator is selected from the group consisting of streptokinase, urokinase, tPA and combinations thereof.
16. The method of claim 1, wherein the plasminogen activator is soluble streptokinase.
17. The method of claim 1, wherein the plasminogen activator is immobilized on a solid support medium comprising SEPHAROSE.
18. The method of claim 1, wherein the low pH, low buffering capacity agent comprises a component selected from the group consisting of an amino acid, a

derivative of at least one amino acid, an oligopeptide which includes at least one amino acid, and combinations thereof.

19. The method of claim 1, wherein the low pH, low buffering capacity agent comprises a component selected from the group consisting of acetic acid, citric acid, hydrochloric acid, carboxylic acid, lactic acid, malic acid, tartaric acid, benzoic acid, serine, threonine, methionine, glutamine, alanine, glycine, isoleucine, valine, alanine, aspartic acid, derivatives thereof, and combinations thereof.

20. The method of claim 1, wherein the buffer is present in the reversibly inactive acidified plasmin at a concentration at which the pH of the acidified plasmin is raised to neutral pH by adding serum in an amount no more than about 5 times the volume of the acidified plasmin.

21. The method of claim 1, wherein the reversibly inactive acidified plasmin solution has a pH between about 2.5 to about 4.

22. The method of claim 1, further including stabilizing the reversibly inactive acidified plasmin by adding a stabilizing agent selected from the group consisting of a polyhydric alcohol, pharmaceutically acceptable carbohydrates, salts, glucosamine, thiamine, niacinamide, and combinations thereof.

23. The method of claim 22, wherein the salts are selected from the group consisting of sodium chloride, potassium chloride, magnesium chloride, calcium chloride and combinations thereof.

24. The method of claim 1, further including stabilizing the reversibly inactive acidified plasmin by adding a sugar or sugar alcohol selected from the group consisting of glucose, maltose, mannitol, sorbitol, sucrose, lactose, trehalose, and combinations thereof.

25. A method for purifying plasmin comprising:

cleaving a plasminogen using a catalytic concentration of a plasminogen activator to yield an active plasmin;

binding the active plasmin to an active plasmin-specific absorbent material to form a bound plasmin; and

eluting the bound plasmin with a substantially neutral pH excipient solution to form a final plasmin solution which is substantially free of degraded plasmin.

26. The method of claim 25, wherein the activated plasmin solution is stabilized by the addition of at least one excipient selected from the group consisting of omega-amino acids and salts.

27. The method of claim 26, wherein the at least one excipient is an omega-amino acid selected from the group consisting of lysine, epsilon amino caproic acid, tranexamic acid, poly lysine, arginine, analogues thereof and combinations thereof.

28. The method of claim 25, further comprising filtering out amino acids from the final plasmin solution.

29. The method of claim 25, further comprising adding a low pH, low buffering capacity agent to the final plasmin solution to form a reversibly inactive acidified plasmin.

30. The method of claim 29, further comprising adjusting the pH of the reversibly inactive acidified plasmin to a pH between about 2.5 to about 4.

31. The method of claim 25, further comprising adding a stabilizer to the final plasmin solution.

32. The method of claim 31, wherein the stabilizer is selected from the group consisting of amino acids, salts or combinations thereof.

33. A process for the purification of plasminogen from a plasma source comprising:
 extracting plasminogen from a plasma paste fraction with a buffer solution at a pH in a range from about 3.5 to 10.5 and collecting the plasminogen-containing solution;
 adding polyethylene glycol, metal oxide, ammonium sulfate, or a combination thereof to the plasminogen-containing buffer solution to precipitate impurities;
 separating the precipitated impurities from the effluent containing plasminogen; and
 adding the effluent containing plasminogen to a plasminogen-specific absorbent material.
34. The process of claim 33, further comprising subjecting the plasminogen-containing solution to cation-exchange chromatography or ultrafiltration/diafiltration prior to addition to the plasminogen-specific absorbent material.
35. The process of claim 34, wherein the solution is subjected to cation-exchange chromatography.
36. The process of claim 33, wherein the plasma source is derived from Fraction II + III of Cohn plasma fractionation process.
37. The process of claim 33, wherein the buffer solution for plasminogen extraction is at a pH in a range from about 7.0 to about 10.5.
38. The process of claim 33, wherein about 1% to about 10% w/w polyethylene glycol or 80g/L to 120 g/L ammonium sulfate is added.
39. The process of claim 33, wherein a particulate metal oxide is added.
40. The process of claim 39, wherein the particular metal oxide is silicon dioxide.
41. The process of claim 40, wherein the silicon dioxide is fumed silica.

42. The process of claim 41, wherein the fumed silica is added in an amount from about 0.1% to about 1.0% by weight of the plasminogen-containing buffer solution.
43. The process of claim 41, wherein the fumed silica is added in an amount from about 0.25% to about 0.5% by weight of the plasminogen-containing buffer solution.
44. The process of claim 33, further comprising adding a plasminogen solubility enhancer.
45. The process of claim 44, wherein the plasminogen solubility enhancer is selected from the group of excipients consisting of lysine, epsilon amino caproic acid, tranexamic acid, poly lysine, arginine, combinations thereof and analogues thereof.
46. The process of Claim 44, further comprising removing the plasminogen solubility enhancer.
47. The process of claim 33, wherein the eluted plasminogen is treated at a pH between about 3 and about 4.
48. The process of claim 33, further comprising stabilizing plasminogen during pH adjustment from about 3 to neutral by adding excipients prior to pH adjustment.
49. The process of claim 33, further comprising removing or inactivating pathogens.
50. The process of claim 49, wherein removing pathogens includes inactivating viral pathogens and removing TSE pathogens.
51. The process of claim 49, wherein viruses are removed or inactivated by the steps selected from the group consisting of heat treatment, caprylate addition, solvent detergent addition, nanofiltration and combinations thereof.

52. The process of claim 51, wherein TSE are removed by the steps selected from the group consisting of PEG precipitation, addition of a particulate metal oxide, depth filtration, nanofiltration, and combinations thereof.

53. The process of claim 33, wherein the plasminogen-specific absorbent material comprises a lysine affinity resin.